Alcohol dependence across the brain; from vulnerability to compulsive drinking

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1

Chapter 1

General Introduction

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Virtually everyone in the Western world has experimented with alcohol during puberty or adolescence. As adults, drinking alcohol is part of the social convention, and taking an alcoholic drink seems to be the rule rather than the exception during parties or other social situations. As a matter of fact, the choice to take a non-alcoholic drink when gathering with friends may raise eyebrows, unless you are pregnant or came by car. Alcohol is everywhere, and next to cigarettes, it is the most frequently used drug in Western society. Although most people can control their alcohol intake, a proportion of the people who start to use alcohol experimentally or occasionally will eventually lose control and can no longer contain or stop their drinking; they drink excessively and may develop alcohol dependence (AD).

Alcohol use disorders (alcohol abuse and alcohol dependence together) constitute an important public health burden worldwide (WHO 2001; WHO 2003), with an estimated 76 million problematic alcohol users (WHO 2004), which is considerably higher than the number of other problematic illicit drug users (Degenhardt and Hall, 2012). Recently it was shown that in Europe alone around 55 million adults (14%) drink alcohol in harmful amounts (Van Amsterdam & Van den Brink, 2013), and 14.6 million citizens (3.4%) suffer from a current alcohol use disorder (Wittchen et al. 2011). Together, alcohol use disorders are responsible for 60-70% of the alcohol-related societal costs (Mohapatra et al., 2010; Van Amsterdam et al., 2013). AD is highly prevalent in the general population with lifetime prevalence 12.5% in the United States (Hasin et al. 2007). Substantial relapse rates are shown with up to 40-60% of initially abstinent alcoholics who have fallen back to excessive drinking within the first few months after treatment, which is as high as 70 to 80% by the end of the first year after treatment (Bradizza et al. 2006; McKay et al. 2006; Walitzer and Dearing 2006). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association 2001), a clinical diagnosis of AD is met when a selection of symptoms is present, including a persistent desire to use, inability to control alcohol use, tolerance, withdrawal, preoccupation with alcohol, and continuation of use despite negative consequences (for all DSM-IV criteria of AD and proposed DSM-5 criteria of alcohol use disorder, see the appendix).

ADDICTION AS A BRAIN DISEASE

The addiction concept has changed during the past centuries. Whereas in the 19th century it was described in a moral model as a choice based on bad values and a weakness of willpower, and it was mainly the judicial system that was concerned with addiction (Heyman 2009), by the mid-20th century, addiction was predominantly studied by medical professionals, and addiction was now considered a disease, instead of a moral deficiency. A symptomatic or psychoanalytic model described addiction as a personality problem, and famous therapists such as Sigmund Freud tried to change the addictive 'personality disorder' with psychotherapy. In the last quarter of the 20th century, under the influence of Ivan Pavlov, learning models have described addiction as inappropriately learned behavior. It was only during the 80's that a biological aspect was defined in the biopsychosocial addiction model, and nowadays addiction is considered to be a chronic and relapsing brain disease (Leshner 1997; McLellan et al. 2000; O'Brien and McLellan 1996).

To study addiction as a brain disease, modern neuroimaging techniques such as positron emission tomography (PET), single photon-emission computed tomography (SPECT) and magnetic resonance imaging (MRI) have advanced in the past three decades, and nowadays constitute key modalities in human addiction research. These techniques help mapping structural, functional, and neurochemical alterations of the brain in substance and behavioral dependencies. One of the most widely used neuroimaging techniques and reported in this dissertation is MRI, which can provide

structural (sMRI) as well as functional (fMRI) information of the brain.

Based on preclinical animal studies and confirmed by these neuroimaging techniques in humans, modern addiction models stress the importance of abnormal brain functioning in the vulnerability, development and continuation of addictive behaviors. However, a key question in addiction research remains what neural mechanisms underlie the fact that some vulnerable individuals undergo a transition from casual, voluntary towards a more chronic and compulsive pattern of drug use, and once developed, why many but not all dependent patients find it so difficult to stop.

Addressing these questions will require some consideration of how vulnerability factors for alcohol dependence as well as prolonged pathological alcohol use affects the brain.

BEFORE DEVELOPING ALCOHOL DEPENDENCE: INCREASED VULNERABILITY

A number of risk factors are known to increase the chance of individuals to get caught in a relapsing spiral of dependence after experimental alcohol use. The most widely studied factors that are known to contribute to the susceptibility to develop AD are the presence of behavioral traits described as disinhibition, poorly controlled behavior or impulsiveness (Haber et al. 2005), early start of alcohol use during adolescence (Grant et al. 2006; Pitkanen et al. 2005), and the presence of familial alcoholism (Cotton 1979; Dawson et al. 1992; Merikangas et al. 1998b; Reich et al. 1988). Moreover, the presence of a family history of AD by itself is associated with disinhibited or impulsive personality traits (Herting et al. 2010; Petry et al. 2002; Saunders et al. 2008), and with an increased probability of adolescents to start drinking at an early age (Prescott and Kendler 1999). Therefore familial AD can be seen as a vulnerability factor at the basis of other, later developing risk factors. Monitoring the presence of first degree family alcohol use disorders could contribute to awareness of a wider range of risk factors.

A family history of alcohol dependence

By now, it is well established that AD runs in families. The risk to develop AD is approximately four times higher for individuals with a family history of AD and other substance use disorders compared with individuals without such a family history (Hasin et al. 1997; Merikangas et al. 1998b; Nurnberger et al. 2004; Reich et al. 1988; Russel 1990; Schuckit et al. 1972). As indicated by twin, adoption, cross-fostering and pedigree analysis studies (Cloninger et al. 1981; Goodwin et al. 1973; Hrubec and Omenn 1981; Merikangas 1990; Reich et al. 1998; Slutske et al. 2002), an estimated 40% - 60% of the risk for AD can be explained by a genetic predisposition (Agrawal and Lynskey 2008; Devor and Cloninger 1989; Enoch and Goldman 1999). This suggests that familial risk magnitude is at least partly determined by underlying biological differences. A substantial remaining percentage could be associated with environmental factors and epigenetics. Indeed, it has been shown that environmental factors associated with a family history of AD, such as bad role models, inadequate psychological support, poor diets, childhood abuse, or maternal alcohol use during pregnancy (Campbell et al. 2009; Gilman et al. 2007; Latendresse et al. 2008; Peters et al. 1994) have a substantial influence on the risk to develop AD later in life. Additionally, once an individual has developed AD, the presence of an alcoholic family history further contributes to a recurrent course and more impairments (Araujo and Monteiro 1995; Milne et al. 2009; Penick et al. 1987), risks that remain even after abstinence (Moriyama et al. 2006).

Mapping neurobiological correlates associated with the increased risk to develop AD, and the influence of familial load of AD in particular, could contribute to our insights into physical factors predating the onset of AD and/or related psychopathology. With this insight preventive strategies could be developed for individuals at high-risk to develop AD.

Neurobiological correlates of a family history of alcohol dependence

Not only does the presence of an alcoholic family history contribute to a high risk to develop alcohol use disorders, it has also been shown to influence both the structural and functional neurobiological profile of these people (Bjork et al. 2008; Heitzeg et al. 2008; Hill et al. 2001; Hill et al. 2009). Structural brain abnormalities have been repeatedly observed in adult patients with alcohol use disorders (Agartz et al. 1999; Mechtcheriakov et al. 2007) and these abnormalities are often interpreted as neurotoxic consequences of chronic excessive alcohol use. Studies in younger samples indicate that gray matter (GM) abnormalities are also present in adolescents with alcohol use disorders, which could suggest neurotoxic damage already at an early age after a relatively brief drinking career. For example, De Bellis and colleagues (2000; 2005) found smaller bilateral prefrontal cortex and hippocampus in adolescent alcoholics compared with age- and gender-matched controls. These findings may be interpreted as related to toxic vulnerability of the developing brain. However, similar GM abnormalities were observed in non-drinking children and adolescents with a positive family history of alcohol dependence (Benegal et al. 2007), actually suggesting that the structural brain abnormalities as previously found in children and adolescents with alcohol use disorders are likely to represent premorbid non-neurotoxic factors associated with a family drinking history. Other MRI studies have shown additional neuroanatomical deficits in high-risk non-drinking FH+ adolescents and children, like smaller right amygdala and cerebellar volume (Hill et al. 2007b), laterality differences in the orbitofrontal cortex (Hill et al. 2009), white matter (WM) volumetric abnormalities of the corpus callosum (Venkatasubramanian et al. 2007), WM microstructure abnormalities across the brain (Herting et al. 2010), and lower structural fronto-cerebellar connectivity (Herting et al. 2011).

Similar to studies on structural brain abnormalities, studies on functional correlates and their related brain activations in individuals at high risk to develop AD show that motivational, emotional, and cognitive functions are challenged under the influence of an alcoholic family history (for a review in adolescents, see Nixon and Tivis 1997). Higher activation of medial prefrontal cortex, cingulate gyrus and ventral limbic regions in response to visual alcohol cues (Tapert et al. 2003) and to the odor of preferred alcoholic drinks (Kareken et al. 2004; Kareken et al. 2010) are positively associated with the presence of an alcoholic family history in alcoholic and non-alcoholic adolescents and young adults under sober circumstances. Alcohol intoxication, however, dampens activation in the medial prefrontal cortex in FH+ but potentiates it in FH– (Kareken et al. 2010). Following this, and based on both human and animal studies on the vulnerability for AD, a model has been proposed which hypothesizes that a genetic predisposition to develop alcoholism, which is largely the case with a family history of AD, involves an initial homeostatic imbalance in the brain, expressed as hyperexcitability/disinhibition towards salient stimuli, which is temporarily alleviated by the ingestion of alcohol (Begleiter and Porjesz 1999). This matches the findings that FH+ individuals show reduced sensitivity to the sedative, dysphoric, and cognitive effects of acute alcohol intoxication compared with FH– individuals (Quinn and Fromme 2011; Schuckit 1985; Schuckit et al. 2004), making them more prone to use larger amounts of alcohol for the same intoxicating effects.

Beside the differentiating acute effects after alcohol intoxication associated with a family history of AD, studies have shown that alcoholic as well as non-alcoholic FH+ individuals show abnormal emotion processing (Acheson et al. 2009; Bjork et al. 2008; Glahn et al. 2007; Hill et al. 2007a), and cognitive impairments such as disinhibition and poor behavioral control leading to increased impulsivity and sensation-seeking (Gierski et al. 2013; Peterson et al. 1992; Petry et al. 2002; Poon et al. 2000; Saunders et al. 2008; Sher 1991). Executive functions were shown to be decreased in adult FH+ individuals, an effect that increases with the amount of alcoholic family members (Gierski et al. 2013). Functional neuroimaging studies in children and adolescents with a family history of AD show abnormal spatial working memory, and related brain activity (Mackiewicz Seghete

et al. 2013). FH+ children who later go on to develop alcohol use disorders show signs of behavioral disinhibition, novelty-seeking, and impulsivity already during their youth (Cloninger 1987; Ernst et al. 2006). Brain areas involved in emotional and cognitive control functions, including nucleus accumbens and orbitofrontal cortex for emotional and reward reactivation, and dorsal prefrontal areas and cingulate gyrus for control functions, show abnormal activity in FH+ individuals (Andrews et al. 2011; Cservenka et al. 2012; Cservenka and Nagel 2012; Heitzeg et al. 2008; Schweinsburg et al. 2004; Silveri et al. 2011; Spadoni et al. 2008). Functional connectivity of frontal control areas have shown to be decreased (Herting et al. 2011; Wetherill et al. 2011), whereas connectivity of nucleus accumbens with paracentral lobule, precuneus and motor areas has shown to be increased and positively associated with sensation seeking in FH+ youth (Weiland et al. 2013), suggesting decreased control over increased reward seeking behavior, a pattern also seen in adult AD patients (see section below).

As can be seen, most family history studies are performed in children, adolescents and young-adults. These findings in young FH+ individuals suggest that, independent of a prolonged drinking history, family status is of influence on regional brain volumes, neurobiological function, and neural connectivity through genetic, epigenetic, or environmental factors. However, it is known that the adolescent brain has not reached full maturation yet (Jernigan et al. 1991).

Therefore a question remains whether observed abnormalities in youngsters either represent a familial transmitted transient delay in brain maturation or a persistent (familial) risk factor for the development of AD. Until now, direct anatomical and functional evidence for the permanent effects in the adult brain of the alleged genetic and environmental influences mediated by familial AD is scarce. A better understanding of the biological factors associated with a family history of AD in the matured brain may prove invaluable for identifying the underlying pathology of addiction vulnerability and for developing more effective substance abuse treatment and prevention programs.

AFTER DEVELOPING ALCOHOL DEPENDENCE: A CHRONIC RELAPSING DISORDER

Once developed, AD and other drug addictions are characterized by a maladaptive and compulsive pattern of alcohol use despite negative consequences (American Psychiatric Association 2001; Heilig et al. 2010; Koob and Volkow 2010). AD can be viewed as "the endpoint of a series of transitions from initial voluntary drug use through the loss of control over this behavior, such that it becomes habitual and ultimately compulsive" (Everitt et al. 2008). Alcohol intoxication brings along a wide range of direct effects, like sleepiness, motor impairments, and memory loss. Next to the critical modification of brain functioning after acute alcohol use (Goforth and Fernandez 2012), prolonged intake of large amounts of alcohol has long-term neurotoxic consequences, and leads to chronic changes in brain structure and function, which persist long after the person has stopped using alcohol. These long-term changes further contribute to an inability to stop drinking and subsequently to relapse.

Based on extensive animal and human research in substance use disorders, several addiction models have been used to explain how addictive behaviors develop in the brain, and endure with a chronic, relapsing character (for reviews see Everitt and Robbins 2005; Koob and Volkow 2010; Volkow et al. 2012). Sensitized motivational processes, increased automatic and conditioned responses, and compromised cognitive control processes have been described, together contributing to the escalation from initial experimental to chronic compulsive alcohol use.

Several models consider the motivational or reinforcing aspects of drug use to be the

main drive to abuse drugs. For example, the theory of incentive sensitization (Robinson and Berridge 1993) states that drug cues acquire incentive saliency when repeated exposure to drugs or drug-related cues enhances the memory of the expected reward. In other models negative reinforcement becomes important when drug intake is reinforced by the avoidance of aversive consequences induced by drug withdrawal, as described by an opponent process theory of motivation (Solomon 1980; Solomon and Corbit 1973), and its neurobiological associate concept of "allostatic load" as described by the classical avoidance theories (Ahmed and Koob 1998; Koob et al. 1993). Although these latter theories of allostasis also may contribute to the critical problem of chronic relapse even after prolonged periods of withdrawal, in general (negative) reinforcement theories are mainly applicable in relapse to drug and alcohol dependence during withdrawal of the body and the brain right after abstinence. Reinforcing properties of drugs are thought to become less important with progressive drug use. Additionally, the initial importance of the rewarding properties of drugs, as is emphasized by several exposure theories such as the incentive sensitization theory, does not always seem to be the main drive towards addiction. Already in the 1960's, studies by Chein and colleagues (1964) questioned the concept of addiction as a consequence of rewarded behavior. They showed that a large amount of healthy individuals who had received drugs, found the effects pleasurable, however they did not become compulsive drug users. Furthermore, they showed that a percentage of dependent patients found the initial drug experience unpleasant, but had become addicted anyway. Other processes, more persistently contributing to the chronic character of AD and putting less emphasis on the (direct) reinforcing effects of drugs are therefore thought to underlie increased vulnerability to relapse after weeks, months or even years of abstinence. Therefore, according to habit formation theories, addiction is often described as the development of a drug-taking 'habit', where behavior has become automatized, highly stimulus bound, inflexible, and insensitive to outcomes such as (positive or negative) rewards (Everitt et al. 2008; Everitt and Robbins 2005), rendering the aspect of reinforcement of no importance in drug-taking habits. Even though the process of habit formation has by some actually also been considered a process of allostasis (Koob and Le Moal 2008), in abstinent substance dependent people, drug-related stimuli can trigger drug-taking habits long after withdrawal effects have gone, leading to relapse even after long periods of abstinence.

The motivational drug use models and the theory of habit formation should, however, not be seen as opposites, but can rather be put in a timeframe of progression, where during the development of the disorder drug taking habits take over, at the expense of reinforcement-guided behavior. This view on addiction as a progression over time has its origin in preclinical animal studies (Everitt et al. 2008; Everitt and Robbins 2005; Vanderschuren and Everitt 2004), but was recently also proposed in the human addiction literature (Koob and Volkow 2010) and has become an important element in the description of addiction staging (van den Brink and Schippers 2012). Therefore below I will discuss the reward, or goal-directed drug taking and drug taking habits as two ends of a continuum, shifting from the former to the latter mediated by prolonged use, a time-dependent progression of drug dependence.

Alcohol dependence: A progression from reinforcement to compulsive habits

As the incentive sensitization model states, through Pavlovian conditioning drug-related stimuli acquire increased saliency (Robinson and Berridge 1993), which results in over-activation of the reward and motivational circuits in the brain when confronted again with addiction related stimuli, in turn initiating drug-related responses such as cue-reactivity and craving (Franken 2003; Monti et al. 1987; Wiers et al. 2007). Consequently, presentation of these cues alone can act as a motivator for reward-seeking behavior, and cue-elicited craving is suggested to play a role in theories of relapse (Tiffany and Carter 1998).

In terms of classical conditioning, cues that are initially associated with Pavlovian conditioning gradually induce instrumental behavior, known as PIT or Pavlovian–to–Instrumental Transfer (Dickinson et al. 2000). According to dual-systems accounts, two dissociable learning processes can be identified in instrumental behavior (de Wit and Dickinson 2009; Dickinson and Balleine 1994); goal-directed behavior and habit-guided behavior. Instrumental drug seeking is first thought to be goal-directed, where the rewarding value of drugs guide the behavior, whereas during the development of drug addiction a gradual shift takes place, where drug seeking behavior becomes progressively habitual (Everitt et al. 2001; Everitt and Robbins 2005; Redish 2004; Volkow et al. 2006a). Goal-directed actions are performed in order to achieve desirable goals (positive reinforcement, as described by several motivational addiction models) or to avoid undesirable outcomes (negative reinforcement, as described by the classical avoidance theories). In the goal-directed system, cues in our environment (stimuli; S) make us think of our goals (outcome; O), which in turn remind us of the responses that have yielded these in the past (response; R) (see figure 1.1, top). Habitual behavior, however, is directly triggered by cues in the environment even when the outcomes have lost their goal value (Balleine and Dickinson 1998). Hence, when habits are formed, the outcomes or rewarding values of an action gradually lose their value, and are no longer taken into account. Instead cues, or stimuli, directly guide the action (see figure 1.1, bottom). Therefore in terms of habit formation, addiction theories considering the rewarding effects of drugs are no longer applicable when it is mainly S-R habitual behavior driving drug use. Habitual responses are quick and automatic, but also relatively inflexible. In healthy circumstances, habit formation is a necessary and adaptive process, to learn to perform behavior in an automated way, for efficient and fast execution of actions. However, a shift from goal-directed towards habitual control has been hypothesized to underlie maladaptive chronic compulsive drug-seeking in substance use disorders like AD (Newlin and Strubler 2007). Indeed, long-term drug seeking in rodents is insensitive to decreasing outcome values, also known as outcome-devaluation (Dickinson et al. 2002; Miles et al. 2003) which suggests the development of habitual behavior.

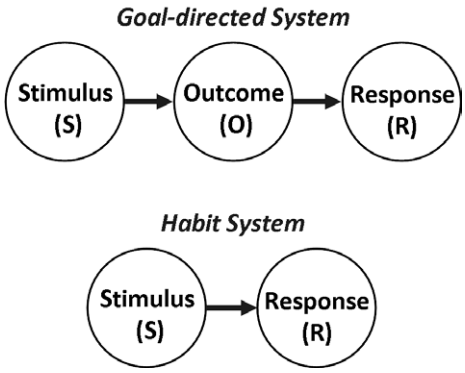

Figure 1.1 Two dissociable learning processes that are identified in instrumental behavior according to dual-systems accounts. During instrumental learning in the flexible goal-directed system (top), the outcome (O) is represented in the associative structure, allowing incentive evaluation of the outcome to impact on action selection (response, R) after a salient cue or stimulus (S). In the habit system (bottom) behavior is directly triggered by environmental stimuli via S-R associations, rendering action selection relatively efficient but also inflexible. Source: de Wit et al. 2009.

In laymen's terms, drug 'liking' during initial experimental drug use shifts towards drug 'wanting' and 'needing' when drug-induced hypersensitivity of motivational circuits drive pathological drug seeking (Robinson and Berridge 2008). Eventually, in the end stage of the development of drug dependence, when drug-taking habits have taken over and the rewarding value of drugs is no longer of importance, a 'must do' state has taken over, contributing to the compulsive character of drug dependence.

While the progression of drug dependence from initial reward driven towards habit driven drug use is characterized by automatic, sometimes unconscious drives, we should bear in mind that

humans to some extent are thought to be characterized by the ability to control these automatic drives through top-down control. However, self-control, or the ability to inhibit urges and control behavior, is thought to be compromised in substance dependent patients (Feil et al. 2010). In combination with sensitized reward processes leading to excessive motivation to take drugs and eventually increased habitual drug taking, cognitive control deficits lead to an inability to control and inhibit these automatic pre-potent responses initiated by the motivational and habit systems (Brewer and Potenza 2008; Jentsch and Taylor 1999; Lubman et al. 2004; Robinson and Berridge 2003; Vandermeeren and Hebbrecht 2012).

This combination of an enhanced drug-using drive and a compromised control system leads to a vicious cycle of craving, bingeing, intoxication and withdrawal (Goldstein and Volkow 2002), which in turn contributes to the chronic character of substance use. Associated with decreased cognitive control, and often seen in substance dependence, are excessive risk taking, sensation seeking, and increased impulsivity, leading to impaired response inhibition and impulsive decision making (Baler and Volkow 2006; Goldstein and Volkow 2002; Perry and Carroll 2008; van Holst and Schilt 2011). These impaired inhibiting mechanisms leading to increased impulsivity are shown on the one hand to be a pre-existing trait or vulnerability factor for the development of drug dependence (Dalley et al. 2007; Haber et al. 2005; Verdejo-Garcia et al. 2008) and on the other hand to be a result of detrimental effects of chronic drug use (Bechara 2005; Jentsch and Taylor 1999). It remains unclear, however, if the impairments in cognitive control functions like inhibition of prepotent responses due to alcohol use actually become more pronounced with a longer lasting history of AD.

Habit formation and control functions in the brain

The meso(cortico)limbic dopamine system (see figure 1.2) plays a main role in the positive reinforcement of drugs of abuse (Koob and Le Moal 2001; Le Moal and Simon 1991; Robbins and Everitt 1999). Triggered by dopaminergic input from the ventral tegmental area (VTA) in the midbrain, salient drug-cues activate ventral parts of the striatum, such as the nucleus accumbens (Schultz 1998) (for a review on the neural correlates of cue-reactivity, see (Heinz et al. 2009)). However, after prolonged drug use, dopamine reactivity in the nucleus accumbens associated with the rewarding effects of drugs has been shown to be dramatically decreased in rodents (Mateo et al. 2005). This matches the idea that drug use behavior shifts away from Pavlovian towards instrumental learning processes, and within instrumental conditioning away from goal-directed behavior towards S-R habits. Behavioral neuroscience studies with rodents have shown that the dorsomedial striatum and the prelimbic cortex subserve goal-directed actions (Balleine and Dickinson 1998; Corbit and Balleine 2003; Killcross and Coutureau 2003; Yin et al. 2005b).

Imaging studies in healthy human volunteers indicate that goal-directed control is driven by activation of the ventromedial prefrontal cortex (VMPFC) (de Wit et al. 2009; Valentin et al. 2007), an equivalent of the animal prelimbic cortex, and by the head of the caudate nucleus (Tanaka et al. 2008), possibly seen as an equivalent of the animal dorsomedial striatum.

When it comes to the neural correlates of habit formation, lesion and microdialysis studies in healthy animals show that the formation of habits is associated with a shift from involvement of the prelimbic cortex towards the striatum (Everitt and Robbins 2005) (see figure 1.3). Additionally, a dopamine-dependent cascading loop (Haber et al. 2000) from the ventral to dorsal parts of the striatum is implicated in the course of habit formation, resulting in the implication of the dorsolateral striatum in mediating stimulus-response (S-R) habitual behavior (Packard and Knowlton 2002; Yin et al. 2004). Conditional rule learning, a basis of habit formation, has been shown to be impaired by lesions of the dorsal striatum and the interruption of its dopaminergic innervations (Reading et al.

1991; Robbins et al. 1990). Striatal cell recordings in animals show that the dorsal striatum may be divided into associative and sensorimotor regions, and these distinct areas may play distinct roles in instrumental learning, with the former involved in goal-directed action-outcome associations and the latter in habitual stimulus-response (S-R) associations (Graybiel 1998; Hikosaka et al. 1999).

In humans, the neural correlates of habits have been studied less frequently, but the few studies performed in healthy populations have shown that habitual behavior mainly involves dorsal striatal areas (de Wit et al. 2009), like the posterior putamen (Tricomi et al. 2009). A recent connectivity study in humans (de Wit et al. 2012b) showed that estimated white matter tract strength between caudate and VMPFC predicted goal-directed action, whereas white matter tract strength between posterior putamen and premotor cortex predicted habitual control.

In the case of long-term drug seeking, increased involvement of the dorsolateral striatum has repeatedly been shown in rodents (Belin and Everitt 2008; Ito et al. 2002; Vanderschuren et al. 2005) and non-human primates (Porrino et al. 2004), mediated by phasic dopamine release (Kienast and Heinz 2006). However, knowledge on the neurobiological mechanisms underlying the shift from goal-directed towards habitual drug-seeking behavior in human drug abusers is scarce. In addicted human populations, PET studies have shown that in chronic cocaine abusers drug cues

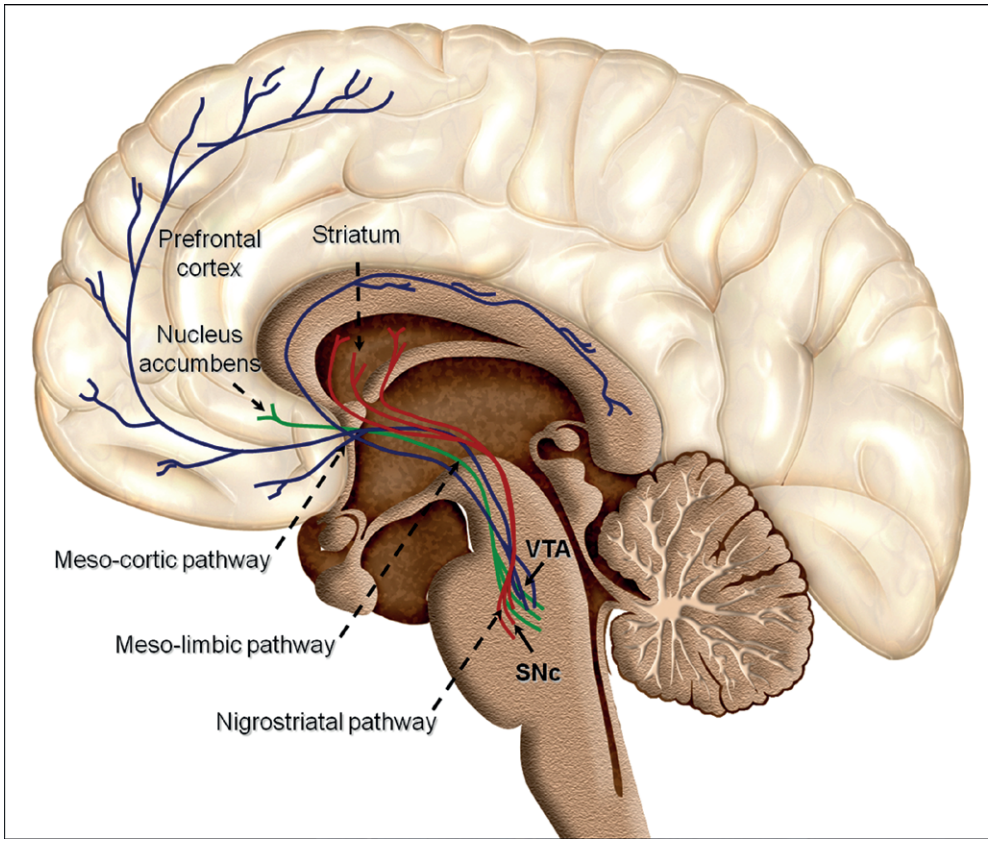

Figure 1.2 Dopaminergic reward structures in the human brain. Dopaminergic neurons are located in the midbrain structures substantia nigra (SNc) and the ventral tegmental area (VTA). Their axons project to the striatum (caudate nucleus, putamen and ventral striatum including nucleus accumbens), the dorsal and ventral prefrontal cortex. Red: Nigrostriatal pathway; Green: Meso-limbic pathway; Blue: Meso-cortical pathway. Source: Arias-Carrion et al. 2010.

significantly increased dopamine in dorsal striatum. These increases were also associated with cocaine craving (Volkow et al. 2006a; Volkow et al. 2008; Wong et al. 2006). A recent study in heavy alcohol users attempted to distinguish the involvement of ventral versus dorsal striatum in reaction to visual alcohol stimuli (Vollstadt-Klein et al. 2010). In accordance with the hypothesis of a shift of learning processes from ventral to dorsal parts of the striatum when AD proceeds, it was shown that in heavy drinkers (most with AD), alcohol cues elicited brain activation in dorsal parts of the striatum, whereas social, but not heavy drinkers showed alcohol cue-reactivity in the ventral striatum. Moreover, ventral striatal activation in this study was negatively correlated with compulsive drinking measurements, whereas dorsal striatal activation showed a positive correlation, indicating a decreasing relevance of cue processing in the ventral striatum when alcohol use becomes more compulsive. Interestingly, a very recent coordinate-based meta-analysis, using activation likelihood estimation (Schacht et al. 2013), analyzed 28 imaging studies on alcohol cue-reactivity, and found that reactivity to alcohol cues (visual, odor, taste) in the ventral striatum was typically reported in heavy alcohol users, and less in alcohol dependent patients. This further matches the hypothesis that the ventral striatum is predominantly involved during early stages of (problematic) drug use, whereas with a longer drinking history, cue-reactivity and related drug-use behavior shifts towards more dorsal parts of the striatum.

However, knowledge on the gradual shift from goal-directed towards habitual drug use and its neurobiological correlates is until now almost exclusively based on pre-clinical animal studies (Everitt and Robbins 2005). Its direct, association with duration of AD has, to the best of our knowledge, so far not been examined in humans with specialized experimental paradigms.

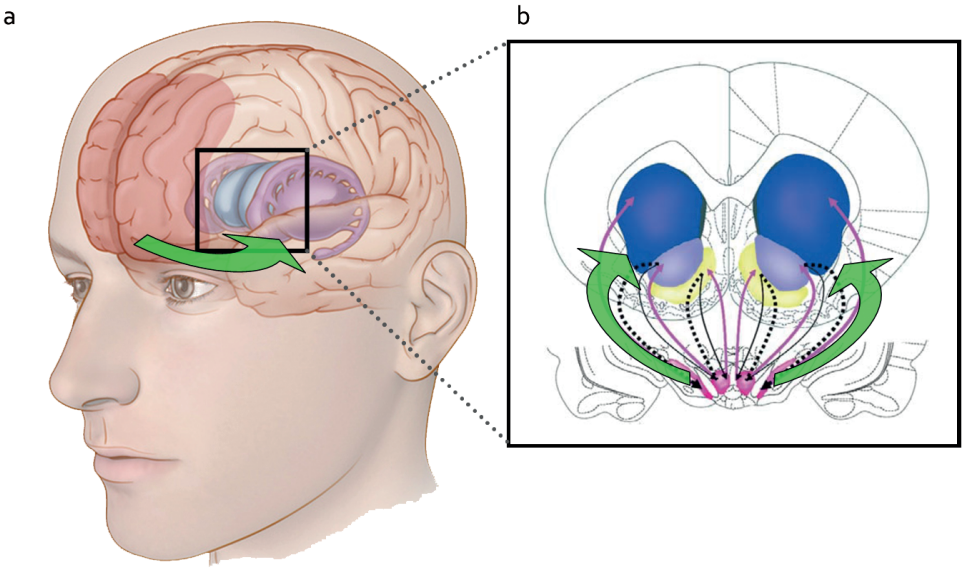

Figure 1.3 Hypothesized neural shifts following prolonged drug use, associated with a shift from goal-directed towards habitual behavior, based on preclinical animal literature. **a.** A shift of main involvement from prefrontal cortical areas towards subcortical areas such as the striatum (depicted in the human brain). Adjusted from: Scott Leighton, Medicus Media. **b.** A coronal cross-section of the rodent striatum, depicting a dopamine-dependent cascading loop between sub-regions of the striatum, from ventral to dorsolateral striatum. Adjusted from: Belin and Everitt 2008.

Additionally, considerable knowledge is available on the neural correlates of cognitive control functions. Next to previously discussed changes in the mesolimbic motivational system, a frontostriatal circuit involved in impulsivity and inhibitory control is shown to be another principal brain system to play a role in the course of substance dependence (Feil et al. 2010; Goldstein and Volkow 2011; Mansouri et al. 2009). Cognitive control functions rely on activity in the dorsal medial and lateral prefrontal cortex, striatum, cingulate cortex, thalamus and (pre-) motor cortex (Cardinal 2006; Chambers et al. 2009). Also connections between prefrontal cortex and ventral striatum (Groenewegen et al. 1999) have shown to be involved in cognitive control functions (Camara et al. 2009). Decreased involvement of dorsal areas of the cingulate cortex, medial- and lateral prefrontal cortex during functions as inhibitory control, conflict monitoring, and decision making in substance dependent individuals (Fu et al. 2008; Salo et al. 2009; Tanabe et al. 2007) confirm a deficit in areas that are part of this control system. Additional to impaired performance in individual brain areas, abnormal frontostriatal functional connectivity was shown to be associated with impairments in decision making (Park et al. 2010) and inhibitory control (Courtney et al. 2013) in alcohol dependence.

However, it remains unclear whether these impaired control abilities further decrease over time, leading to an increased disability to control drug-using drives. Therefore the association with AD duration and severity needs to be further explored.

ALCOHOL DEPENDENCE AND DEPRESSION/ANXIETY DISORDERS

An often overlooked, but very important characteristic of AD, probably more than other substance use disorders, is the high comorbidity with depression and anxiety disorders (Boschloo et al. 2011; de Graaf et al. 2002; Kessler et al. 1997; Merikangas et al. 1998a). A large epidemiologic study showed that having alcohol dependence increases the prevalence of depression, such as major depressive disorder, and anxiety disorders, including generalized anxiety disorder, social phobia and panic disorder, with significant odds ratios ranging from 1.5 to almost 3 (Blanco et al. 2012). Comorbid AD and depression/anxiety was shown to be associated with more severe impairments compared with 'pure' AD (Burns and Teesson 2002; Grant et al. 1996) and less favorable treatment outcomes (Burns et al. 2005; Helzer and Pryzbeck 1988). Additionally, comorbidity with depression and anxiety may complicate the presentation and course of AD. Like all substance use disorders, AD is considered an 'externalizing' disorder, characterized by increased impulsivity, sensation seeking and extraversion, whereas depression and anxiety are characterized by opposite traits, such as decreased impulsivity, introversion and anhedonia, and are therefore considered 'internalizing' disorders (Achenbach 1966; Krueger 1999). Such a combination of externalizing and internalizing psychopathology may contribute to the heterogeneous character of AD in terms of both its etiological components and its phenotypic presentation. This could be expressed at the level of behavioral and neurobiological measurements of impulsivity and reward sensitivity, but likely also when it comes to the reactivity to salient cues, due to the anhedonic negative state of patients with depression and/or anxiety disorders, leading to reduced brain reward responses towards external rewarding cues (Eshel and Roiser 2010; Pizzagalli et al. 2008).

On the other hand, disorders that show high comorbidity and thus are thought to be closely related to each other, may share etiologic factors, clinical course, treatment response, or neurobiological profile. This might point to an underlying structure of genetic or environmental risk, which could be mediated by family factors such as a family history of AD. Indeed, next to a high prevalence of depression and anxiety disorders in established AD, these affective disorders are also

hypothesized to be more common in individuals with a family history of AD (Araujo and Monteiro 1995; Dawson and Grant 1998; Knappe et al. 2009; Nurnberger et al. 2004; Schuckit et al. 1995; Sjoerds et al. 2012b). This implies a role of an alcoholic family history in the development and maybe even the manifestation of depression/anxiety, and possibly in its neurobiological profile based on shared genetic or unique environmental factors (Kendler et al. 2011). An indication that a FH of AD has a differentiating influence on the receptor profile and therefore a more general neurobiological profile of patients with a depression/anxiety is provided by a study showing that depressed patients with a FH of AD had a significantly better anti-depressant response to the NMDA receptor antagonist ketamine than patients without a FH of AD (Phelps et al. 2009).

However, studies performed in AD patients have either excluded patients with comorbid depressive and/or anxiety disorders, thus collecting data on a very specific sample of limited clinical relevance, or failed to consider the presence of comorbid depression and/or anxiety as a potential confounder of the (lack of) observed impairments in AD. And when it comes to alcoholic family history studies, most have typically focused on the risk for, and manifestation of AD in individuals, but not on the presence of related psychopathology like depression/anxiety.

Therefore it is desirable to further study the neurophysiological profile of depression / anxiety both in the context of an alcoholic family history and as a comorbid factor in AD patients.

AIM AND OUTLINE OF THIS DISSERTATION

During this PhD project, we aimed to study a number of key elements of alcohol dependence and their neurobiological correlates. On the one hand a pre-existing risk factor for AD in an as yet non-alcoholic group of adults was examined, whereas on the other hand a group of chronic AD patients was studied with special emphasis on the duration of AD and the associated progression from motivational- to habitual-, and associated control processes. Additionally, since AD is highly associated with depression and anxiety, we considered these disorders in the context of familial alcohol dependence and as a comorbid disorder in alcohol dependent individuals.

After this general introduction regarding the rationale of this dissertation in **section I, chapter 1**, I describe five imaging studies in the two subsequent sections. In **section II** the focus lies on the neurobiological correlates of a family history of AD, or in other words the presence of alcoholic pathology in first-degree (father, mother, brother, sister) relatives of individuals in non-alcoholic adults, i.e. before the start of AD pathology. The samples for this section were drawn from the large Netherlands Study of Depression and Anxiety (NESDA) cohort, containing both healthy controls as well as patients with a depression and/or anxiety disorder.

In the first chapter of this section, **chapter 2**, we studied the influence of an alcoholic family history on the volumes of regional brain structures in non-alcoholic adult individuals. Although studies in young non-alcoholic individuals with a family history of AD have already shown that certain volumetric reductions are present even before the development of problematic alcohol use (Benegal et al. 2007; Hill et al. 2001; Hill et al. 2007b; Venkatasubramanian et al. 2007) it cannot be concluded that these reductions constitute the final risk factor for the development of an alcohol use disorder. The brains of children and adolescents have not reached full maturation yet (Jernigan et al. 1991). Therefore the observed abnormalities in youngsters with a positive family history for AD could be just a transient effect of slow maturation related to a family history of alcohol dependence, and not an enduring risk factor or biological marker for AD. Therefore we used an optimized voxel-based morphometry (VBM) approach to assess regional GM volume in a sample of N = 36

non-alcoholic adults with (FH+) and N = 107 without (FH-) a history of AD, i.e. in subjects that have fully matured brains and who therefore do not suffer from a transient delay in brain maturation. We hypothesized smaller GM volumes in our adult FH+ group, which would likely represent persistent abnormalities associated with familial AD rather than alcohol-related neurotoxicity or a transient neurodevelopmental delay.

In **chapter 3** we further elucidated the influence of a family history of AD on functional brain correlates. In this study we specifically focused on patients that had not developed AD (yet), but had developed depression and/or anxiety disorders, which are known to be highly prevalent in people with a family history of AD. In this chapter we aimed to examine the association between a family history of alcohol dependence and the neurophysiological manifestations of psychopathology other than AD, e.g., mood/anxiety disorders. We studied both cognitive as well as emotional functions using fMRI, and connected the knowledge obtained by the two distinct task paradigms to acquire a broader view on (neuro-) functional correlates of an alcoholic family history within depressed and/or anxious patients. We compared depressed/anxious patients with (N = 31) and without (N = 77) a FH of AD and hypothesized that the presence of a FH of AD would affect cognitive control functions and modulate responsiveness to emotional stimuli, indicated by differences between the FH- and FH+ groups in performance levels and activation in brain areas associated with these functions. To facilitate the interpretation of our findings, differences in performance levels and brain activation between the FH- and the FH+ patient groups were compared with those of 31 healthy controls (HC) without a FH of AD.

In **section III** we focused on the neurobiology of AD in a large sample of alcohol dependent patients. In order to study a sample of AD patients with a wide variety of disease duration and severity, AD patients were recruited from different sources, such as local addiction treatment clinics and the NESDA cohort. We aimed to study the processes that contribute to the development of habitual or compulsive drug use, with an emphasis on the duration of AD. We hypothesized that with longer lasting AD, we would see more habit-like functional correlates, and reduced control capacity.

In the first two chapters of this section we tested whether the hypothesized stronger involvement of habit pathways with prolonged AD could play a role in the development of chronic drug use in alcohol dependent humans. In **chapter 4** we focused on Pavlovian conditioned processes, by studying the association of visual cue-reactivity in the brain and self-reported craving with duration and severity of AD. Additionally we associated cue-reactivity and craving with depression/anxiety disorders by comparing the AD group (N = 30) with a non-alcoholic depression/anxiety group (N = 15) as well as healthy controls (N = 15), and by associating the severity of comorbid depression/anxiety symptoms within the AD group with the outcome measurements.

Our main hypothesis was that there would be a shift of cue-reactivity from ventral to dorsal striatal areas mediated by AD duration. Second, we expected higher cue-reactivity and craving in AD compared with both depression/anxiety patients and healthy controls to be mainly associated with alcohol dependence characteristics such as duration and severity and not, or only weakly, with depression/anxiety.

In **chapter 5** we continued our study of the habit pathways, this time by looking at instrumental learning in AD and its association with the duration of AD. We aimed to examine if an imbalance between goal-directed and habitual control plays a role in the development of chronic drug use, and to our knowledge, we were the first to experimentally study this in substance dependent humans. We examined the balance between goal-directed and habit learning, as well as its neural correlates, in N = 31 abstinent alcohol dependents and N = 19 healthy controls. Moreover, we examined whether this imbalance is dependent on disorder duration to test the theory that initial

goal-directed actions are gradually replaced by stimulus driven habitual behavior.

In **chapter 6** we studied response inhibition, a measurement of motor impulsivity. Even though most substance use disorders are associated with increased impulsivity, studies on impulsivity and response inhibition in alcohol dependence have yielded inconsistent results. This could be due to the frequent comorbidity of AD with mood disorders, the latter having been associated with decreased as well as increased impulsivity and inhibition abilities. Therefore, in the current study, we aimed to distinguish response inhibition impairments in AD patients from response inhibition effects associated with depression/anxiety. We looked at the influence of AD duration and severity and depression/anxiety characteristics within a group of N = 31 AD patients. We compared alcohol dependent subjects with healthy controls (N = 16) as well as with patients with depression/anxiety disorders (N = 18), a comparison that has not been reported before on inhibition parameters.

Finally, in **section IV**, I draw general conclusions on all performed studies. **Chapter 7** provides a general summary and discussion of our main research findings. Methodological considerations and clinical implications will be discussed as well. **Chapter 8** summarizes this dissertation in Dutch.

BOX 1. AIMS OF THIS DISSERTATION

AIM 1 (**section II**): To study the neurobiological correlates of a family history of AD in non-alcoholic adults.

a. (**chapter 2**): How does a family history of alcohol dependence influence brain structure in non-alcoholic adults?
b. (**chapter 3**): How does a family history of alcohol dependence influence emotional and cognitive brain functions in non-alcoholic adults with a depression / anxiety disorder?

AIM 2 (**section III**): To study the neurobiological correlates of processes that contribute to a time-dependent progression towards habitual alcohol use in established alcohol dependent patients.

a. (**chapter 4**): How are Pavlovian alcohol cue-reactivity in the brain and craving associated with duration and severity of AD, and with comorbid depression and anxiety?
b. (**chapter 5**): Is there a higher reliance on stimulus-response habit learning in alcohol dependents, and how is this related to duration and severity of AD?
c. (**chapter 6**): How is response inhibition, and its neural correlates, associated with duration and severity of AD, and with comorbid depression and anxiety?